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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,934	02/24/2006	John W Harmon	001107.00550	3384

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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04/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,934	HARMON, JOHN W	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *8-13,16 and 25-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,14,15,17-24 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 1-28-08.

Claims 1-44 are pending in the instant application.

Claims 8-13, 16 and 25-40 have been withdrawn from prosecution as being drawn to non-elected inventions. Claims 1-7, 14, 15, 17-24 and 41-44 have been examined on their merits as set forth below.

The declaration under 37 CFR 1.132 filed 1-28-08 is insufficient to overcome the rejection of claims 1-7, 14, 15, 17-24 and 41-44 based upon obviousness as set forth in the last Office action and for the reasons set forth below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

This application contains claims 8-13, 16 and 25-40 drawn to an invention nonelected with traverse in the reply filed on 6-6-06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1-7, 14, 15, 17-24 and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Zhang et al (USPN 6,972,013), Glasspool-Malone et al (Mol. Therapy, Vol. 2, pages 140-146 (2000)) and Bureau et al (USPN 6,528,315), the combination in view of Ruben et al (US 2003/0186904), the combination further in view of Arbeit (USPN 6,838,430), Blott et al (US 2007/0141128) and Miller (USPN 4,846,181) for the reasons of record set forth in the Office action mailed 9-27-07.

Applicant's arguments and declaration filed 1-28-08 have been fully considered but they are not persuasive. Applicant argues that the instant rejection is improper because no cited references teach the step of applying an electric field intradermally to wounded tissue. Applicant also argues that, because large differences exist between normal skin and wound tissue, for instance that, among others, wounded tissue has more vascular volume than normal skin, one of skill in the art would not have had a reasonable expectation of success in promoting wound healing in a patient comprising administering a nucleic acid encoding a growth factor to wounded tissue in combination with applying an electric field intradermally. Applicant also points out the differences between wound tissue and normal skin tissue regarding differences in the expression of several growth factor genes, increased vascular volume, increased proliferation at the site of the wound, and increased apoptotic cells. Applicant also argues that, because wound healing was far greater than additive using the instantly claimed combination treatment, it would not have been obvious to perform the instantly claimed method.

The claims are drawn to a method to promote wound healing in a patient comprising administering a plasmid nucleic acid encoding a growth factor operably linked to a promoter, which growth factor is optionally HIF-1α, to a cutaneous wound site, and applying an electric field intradermally to the wounded tissue, which electric field comprises 6-18 square wave pulses, at 400-1800 V/cm, from 100 microseconds to 20 milliseconds in duration, wherein the wound eschar is removed surgically prior to administering the nucleic acid, and wherein the wound is a decubitus ulcer or a burn wound, and wherein the patient is a diabetic.

Contrary to Applicant's assertions, the instant invention would have been obvious to one of ordinary skill in the art by combining what was well known in the art. Applicant asserts that because the combination of delivering a nucleic acid encoding a growth factor and intradermal electric current intradermally to a wound site provides for more than additive wound healing effects, it would not have been obvious to perform this combined therapy. Contrary to Applicant's assertions, the use of growth factors for treating wounds, including burns and other skin disorders in diabetics, and in combination with one or more additional nucleic acids encoding therapeutic agents that promote wound healing, was well known in the art at the time of the instant invention, as disclosed previously by many in the art, including Zhang, Ruben, Arbeit, Blott and Miller. Arbeit teaches the administration of a nucleic acid encoding the growth factor, HIF-1α, to accelerate wound healing in a patient; Ruben was properly relied upon for teaching the use of electroporation for recombinant gene delivery to target cells,

and the use of growth factors for treating wounds, burns and other skin disorders in diabetics, including the administration of the growth factor, KGF-2, in combination with one or more additional nucleic acids encoding therapeutic agents that promote wound healing; Zhang was properly relied upon for teaching intradermal delivery of plasmid DNA encoding at least one growth factor for acceleration of wound healing, followed by electroporation using single square wave pulses between 100-500 V/cm, between 5 microseconds and 99 milliseconds; Blott was properly relied upon for teaching the importance of the expression of nucleic acids encoding therapeutic molecules at a wound bed and at the edges of a wound for promoting efficient healing, especially for diabetic foot ulcers and decubitus ulcers; and Miller was properly relied upon for disclosing the well known, historical approach of applying pulsed electrical fields intradermally to wounded tissues for promoting wound healing in a subject (see, e.g., Miller at col. 6, lines 13-18: "[T]reatment with pad placement (sponge) directly into the wound, directly over a saline soaked 4 X 4 gauze, into the wound directly over semi-occlusive dressings, or directly over a saline dressing; treatment with an immersible electrode..." (emphasis added).

In addition, electroporation (or delivering electric current to target cells) was a well known way of enhancing delivery of nucleic acid molecules to target tissues at the time of the instant invention, as disclosed previously by many in the field, including Zhang (discussed above), Glasspool-Malone and Bureau. Glasspool-Malone disclosed improvements in applying an electric field intradermally for enhancing delivery of nucleic acids to cells in a subject; and

Bureau was properly relied upon for teaching the delivery of nucleic acids encoding growth factors to target cells using electroporation the conditions instantly claimed, e.g. using an intensity between 200 and 600 V/cm for a total duration greater than 10 milliseconds, with square wave pulses from 1- 1000 pulses.

So, contrary to Applicant's assertions, it would be obvious to one of ordinary skill to provide current intradermally to wound tissue, both for enhancing nucleic acid delivery and for enhancing wound healing in the absence of administering nucleic acids encoding growth factors, relying on the teachings outlined above. Furthermore, it would not have been surprising that applying growth factors, which were well known to aid in wound healing at a wound site, combined with using a delivery system that is well known to enhance delivery to and gene uptake by target tissues, including wound tissue, would provide for enhanced healing effects. Contrary to Applicant's assertions, the results of enhanced treatment results using these combined methods would be expected by one of ordinary skill in the art, and the finding that the treatment effects are more than additive, as argued by Applicant, does not automatically render the instant invention free of the prior art or non-obvious. Furthermore, Applicant argues limitations that do not exist in the claims (i.e. obtaining synergistic effects).

In addition, Applicant's arguments and the declaration filed 1-28-08 discuss the findings of Lokmic et al (Wound Rep. Reg. 2006, 14: 277-288), pointing out differences between normal and wounded tissue, and illustrate the

differences in such things as vascular volume, cellular proliferation, and enhanced expression of some growth factors in wounded tissue compared to normal tissue. Contrary to Applicant's arguments, the wound tissue characteristics discussed by Lokmic, of enhanced growth factor expression and vascular volume, etc... by wound tissue, illustrate more profoundly why there would have been a reasonable expectation of success by a skilled artisan to provide for enhanced delivery to wounded tissue (e.g. because it is more highly proliferating and has higher vascular volume) compared to normal skin tissue. What's more, since there has been a well known correlation between enhanced growth factor expression at the site of wound healing, more efficient delivery of growth factors to a wound site would have been expected to bolster the healing process. It is therefore unclear how the findings of Lokmic teach away from, or otherwise provide any surprising results, thereby rendering the instant invention free of the prior art.

One of ordinary skill in the art would have expected that the application of electric current under the well known and previously described conditions set forth by Zhang, Glasspool-Malone, Bureau, Ruben and Miller would have enhanced delivery of wound healing therapeutics to the wound site and enhance the healing process. One of ordinary skill in the art would have expected that the delivery of nucleic acids encoding growth factors including HIF-1α and KGF to the site of the wound, including to the peripheral wound tissues and intradermally, would enhance the healing process because the use of these growth factors in wound healing had been taught previously by Zhang, Ruben

and Arbeit. What's more, Blott and Miller had taught that the allogeneic wound healing factors and polypeptides (present at the sight of the wound) also enhance wound healing after application of electric current to the wound area.

For these reasons, the instant rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or

applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
4-21-08

/Jane Zara/

Primary Examiner, Art Unit 1635